Remarks

The claims pending in this application are 1, 2, 4-27, and 29-34. All claims stand rejected and/or objected to. Claims 1, 12-15, 23, 27, 29, 30 and 33 are amended. Claims 2 and 31 are cancelled. The claims remaining of record for examination are claims 1, 2-27, 29-30, 32-34. It is urged that all claims remaining of record are in condition for allowance as all grounds for objection or rejection are addressed and overcome herein.

I. Claim Objections

Claims 12-15 and 31 are objected as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 12-15 are hereby amended to recite the step of providing the marker with said medication of claim 1 for the patient to take in a particularly prescribed and preferred manner which limits claim 1 in that claim 1 merely recites the medication without the limitation of the preferred manner for the patient to take the medication. Claim 31 is hereby cancelled. Accordingly, the objections as to these claims may be withdrawn.

II. Claim Rejections

1. 35 USC §112, ¶1

Claims 1, 2, 4-27, 29 and 30 stand rejected under 35 USC 112, first paragraph, because the specification, while acknowledged as "being enabling for providing a medication that itself comprises the marker", is said to fail to "reasonably provide enablement for providing a combination of a medication and an [sic. a] marker so as to detect the present [sic presence]/absence of the odorous

marker to indicate compliance/non-compliance in taking the medication." The Examiner insists that the marker must be part of the medication if there is to be an operative correlation between detection of the marker and adherence in taking the medication.

In light of all of the teaching in the specification, such an interpretation of the claim is not tenable. Nonetheless, Claim 1 is hereby amended to clarify that the medication comprises the marker and at least one therapeutically active agent, and that the combination of the maker and the at least one therapeutically active agent in the medication is "such that said marker and said at least one therapeutically active agent are taken by said patient concurrently". This amendment to the claim makes it clear that the patient is not being provided with two separate items which may be taken independently of each other. Therefore, detection of the marker clearly correlates with the taking of the medication. Support for this limitation is found throughout the application. The application makes it plain that the term "medication" implies both the active pharmaceutical ingredient (the "API") and any excipients, markers, including but not limited to odorous or olfactory markers and the like. The Abstract of the disclosure states that the "markers result either directly from the medication itself or from an additive combined with the medication." See likewise the disclosure at paragraph 0003, and 0017. Again, this cited disclosure is not the exclusive disclosure in the specification which makes it plain that the term "medication" includes the API, which itself may give rise to a detectable marker, or the marker may be a compound which is included with the API as part of "the medication". See also the legend of Figure 2, which states "PCMS includes marker compound included in medication that is exhaled into detection system for accurate and reliable

monitoring off-site." See, likewise, the legend of Figure 3, which states: "Step 1 - Medication is taken, releasing Marker Compound". Likewise, for Figure 4, for which the legend states: "PCMS includes marker compound included in medication that is exhaled into detection system for accurate and reliable monitoring off-site." Thus, it is incorrect to state that the "currently recited method is not operable in detecting if the medication has/has not been taken as it only tests if the odorous marker has/has not been taken", as the marker is part of the medication, and according to the claim as herein amended, is taken concurrently with the therapeutic agent the adherence in taking of which is being monitored.

Further, the summary of the invention, (page 3, lines 29-30) the following text appears:

"In other embodiments, the therapeutic drug marker is an additive, or a metabolite of an additive, that is administered concurrently with a therapeutic agent to a patient."

This text makes it clear that the marker and drug are administered concurrently, not, as the Examiner is suggesting, independently of each other.

The term "concurrent" is defined at page 7, lines 20-30, which definition again makes it clear that there is sufficient association between the marker and active therapeutic agent that detection of the marker necessarily confirms compliance in taking the active therapeutic agent:

'"Concurrent" administration, as used herein, refers to the administration of a therapeutic drug marker with a therapeutic

agent in accordance with the systems and methods of the invention for monitoring patient compliance with a prescribed regimen. By way of example, a therapeutic drug marker can be provided as an additive in admixture with a therapeutic drug, such as in a pharmaceutical composition/medication; or the marker and therapeutic drug can be administered to a patient as separate compounds, such as, for example, separate pharmaceutical compositions administered consecutively, simultaneously, or at different times. Preferably, if the marker and the therapeutic drug are administered separately, they are administered within sufficient time from each other so that the concentration of the marker in exhaled breath is an accurate indicator of the concentration of the therapeutic drug in the patient's blood stream.'

Accordingly, no new matter has been added. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 32 is rejected as failing to comply with the written description requirement with the recitation of "the marker is a combination of markers combined as an additive with the medication" being alleged to be new matter.

This is not correct. The field of the invention of the subject application provides:

"Field of Invention

The present invention relates to marker detection for monitoring patient compliance, and, more particularly, to a method and system for detecting in a bodily fluid sample **markers** associated with a therapeutic agent, wherein the markers are derived either from the therapeutic agent or from **an additive combined with the therapeutic agent**."

This clearly recites additive and "markers" in the plural.

The summary of the invention provides:

"Summary of the Invention

The present invention solves the needs in the art by providing methods and systems for monitoring drug compliance by detecting markers, such as odors, presented in a patient after scheduled administration of a prescribed medication. Such **markers** result either directly from the therapeutic drug or from an **additive combined with the drug**. "

This text again references "markers" in the plural and that these are provided as an additive combined with the drug.

Further in the summary of the invention, (page 3, lines 29-30) the following text appears:

"In other embodiments, the therapeutic drug marker is an additive, or a metabolite of an additive, that is administered concurrently with a therapeutic agent to a patient."

See also page 4, lines 1-5, which provide: "Preferably, the therapeutic agent and additive are metabolized by the patient. To assess whether the patient complies with the prescribed therapeutic drug regimen, a sample of the patient's bodily fluid (*e.g.*, exhaled breath) is analyzed to detect the therapeutic drug marker, which (in these embodiments) is either the additive or a metabolite of the additive, or a combination of the two."

See also page 5, lines 25-30:

"The **therapeutic drug markers** of the invention are derived either directly from medication comprising the therapeutic agent or from an **additive combined** with the medication. Such markers preferably include volatile or olfactory markers (odors) as well as other substances and compounds that may be detectable by various methods, as described in more detail herein."

See also page 6, lines 21-26:

"The following are markers that can be detected in exhaled breath in accordance with the subject invention: a therapeutic drug, a metabolite of a therapeutic drug, **an additive that is concurrently administered** with a therapeutic drug, or a metabolite of an additive that is administered concurrently with a therapeutic drug. Preferred therapeutic drug markers include volatile and/or olfactory markers (odors) as well as other substances and compounds, which may be detectable by sensors of the subject invention."

And so forth. Reconsideration and withdrawal of this ground for rejection is respectfully requested.

2. 35 USC §112, ¶2

Claims 1, 2, 4-27 and 29-34 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission assertedly "amounting to a gap between the elements." The basis for this rejection is the same as that addressed above in connection with the rejection under 35 USC 112, first paragraph, namely, the purported need to include in the

marker in the medication . Applicants urge that this issue has been resolved above, and therefore this rejection may be withdrawn.

It is noted, in any event, that the Examiner has conceded that claims 2, 9, and 10 as they stood prior to issuance of the outstanding Office Action contained the relevant limitation and therefore should not have been subject to this ground for rejection. Further, claim 1 is explicit in requiring "a combination of a medication and a marker" and is herein further amended to make it clear that the marker and medication are taken concurrently. Reconsideration is requested.

Claims 23-25 are rejected as being indefinite. The Examiner has suggested rewording of the claims to recite active methods steps. These claims are herein amended to address and overcome the stated rejection by placing additional limitations on the features of the marker utilized according to the claimed method. The Examiner's invitation to reword the claims with the relevant limitations in the form of active steps is not accepted because then the claim might be interpreted to require additional affirmative steps by the patient, whereas, in fact, by appropriate choice of the marker, the action of various metabolic processes naturally proceeds without any further required volitional step by the patient. It is urged that the amendments that have been made to these claims remove any alleged indefiniteness.

Claim 29 stands rejected as being incomplete for failing to include steps relating to how the medication combined with the detectable marker is produced. Claim 30 is said to fail in further limiting the method of producing the medication with further steps that provide for it being a transdermally delivered medication, and

reciting an intended use.

In response, claim 29 is herein amended to recite appropriate steps with reference to the specification at page 22, lines 23-30, which provides:

"In one embodiment, the therapeutic drug marker will coat the oral cavity or esophagus or stomach for a short while and be exhaled in the breath (or in a burp). For drugs administered in the form of pills, capsules, and fast-dissolving tablets, the markers can be applied as coatings or physically combined or added to therapeutic drug. Markers can also be included with therapeutic drugs that are administered in liquid form (*i.e.*, syrups, via inhalers, or other dosing means). Certain therapeutic drug medications can have a coating to prevent the therapeutic drug marker from dissolving in the stomach and enable detection of the marker in exhaled breath."

Claim 30 actually depends from claim 1 rather than from claim 29, and therefore is not directed to a method of producing a medication. Claim 30 is, nonetheless, amended to positively recite the limitation requiring transdermal delivery, thereby clearly further limiting the method of claim 1 by requiring this mode of administration.

Claim 33 is rejected as being indefinite because it is alleged to be unclear as to what is meant by the recitation that more than one medication is included in the medication. Claim 33 is hereby amended to clarify that more than one therapeutically active agent is required to be included in the medication in order to come within the scope of this claim. It is believed that this amendment

addresses and eliminates any alleged indefiniteness in this claim as well as the appropriate interpretation of prior art which would or would not read on this claim

3. 35 USC §102(e):

Claims 1, 2, 7-21, 23-27, 29-31 and 34 stand rejected as being anticipated by Katzman (5,962,335). Applicants respectfully traverse.

The Office characterizes the Katzman reference in several respects which are believed to be inaccurate. In addition, the Office appears to have accorded little or not patentable weight to the arguments advanced in the prior response which pointed out that per the Katzman reference, there can be no doubt about whether a patient has taken a medication, the metabolism of which is to be studied according to the methods disclosed by Katzman, while in the present invention, the very thing that is a predicate to the Katzman reference, i.e. the taking of a medication, is the thing which is in doubt and which the present technology is directed to providing a methodology for determining. In order to be sure that this distinction is accorded appropriate patentable weight, claim 1 is herein substantially amended to make it clear that the method of this invention has no application to a situation, as in Katzman, where there is no doubt as to whether a particular medication has been taken or not. Application of the present invention to Katzman would make no sense whatever, as in that situation, the failure to take a medication has been ruled out as a variable. This is emphasized in the currently amended claim by specifying, in the preamble, that this invention is: "A method to determine whether a patient has taken a medication". The steps of the method now

include the specific elements of "analyzing the sample of the patient's breath utilizing an instrument adapted to detect said marker detectable in gaseous exhaled breath to ascertain the presence or absence of said marker in the patient's breath, where the presence of the marker is an indication that the patient has taken the medication and the absence of the marker is an indication that the patient has not taken the medication", and the step of "based on the analysis, determining whether the patient has taken the medication or not."

None of these steps or elements make any sense in connection with the metabolic studies and methodology disclosed per Katzman and form no part of what Katzman discloses.

In addition, claim 1 is herein amended to include the clarification that the medication includes a marker "which is not chemically part of the active therapeutic agent itself", and claim 2 which provided for such to be the case is herein canceled. It is urged that these amendments should not have been required in light of the other elements and distinctions in the claim, as pointed out above, but these amendments are made to remove any possibility of confusion and to secure allowance.

Respectfully, it is urged that the Office mischaracterizes Katzman in the outstanding Office Action at pages 7-8 in at least the following ways:

1. The Office Action states that "Katzman discloses a breath test for detection of drug metabolism (abstract; column 1&2). Katzman discloses that a safe and effective amount of the drug, isotopically-labelled (**additive to the drug; also considered a**

coating as it is applied on the drug), is administered to a subject."

Respectfully, inclusion of an isotopic label cannot properly be characterized as providing an additive to a drug or a coating to a drug because it is applied on the drug. Inclusion of an isotopic label in a drug represents, rather, a fundamental chemical change to the therapeutically active agent itself. This is a point that was made out extensively in the prior response in this case, at pages 15-16, where the Applicant pointed out that were the methodology of Katzman to be applied to the field of drug compliance monitoring, this would have the distinct disadvantage of requiring that for each new drug the taking of which is to be monitored, an entire new regulatory approval would need to be undertaken because the inclusion of an isotopic label in the drug represents the production of a new chemical entity the equivalence of which to an existing and regulatorily approved therapeutically active agent would need to be proven anew. By contrast, according to the present invention, where the taking or not of a particular therapeutically active agent is to be monitored by tracking a surrogate included in the medication with the therapeutically active agent, no change in the regulatory approval pathway would be required for the therapeutically active agent, and provided that the particular marker that is included in the medication with the therapeutically active agent is one which itself has been approved, then the entire process for regulatory approval for such trackable medications is simplified, expedited and made much more economical.

Accordingly, it is respectfully requested that the Examiner should carefully reconsider and withdraw this characterization of the isotopic modification employed by Katzman as it is applied

against the instant invention.

2. This incorrect predicate having been laid, as outlined in point 1 above, the entire characterization of Katzman at page 7 of the outstanding Office Action is faulty. For example, the statement that "Katzman also discloses that the label used to identify the metabolite in the exhaled breath of the subject should at least be present on a portion of the drug that forms the metabolite (columns 7 and 8; lines 22-26, col. 6)" would, per the predicate previously laid, seem to support the Office's contention that this bears some novelty defeating relationship to the present claims. However, this cited teaching of Katzman in fact explicitly demonstrates the distinction from that which is claimed in the present application, particularly in light of the clarifying amendments to claim 1 that have been introduced per this amendment. That is, the use of an isotopic label as part of the therapeutically active agent, including in a portion of that molecule which is tracked during metabolism of the therapeutically active agent, is explicitly excluded from the claims.

3. In light of what is discussed above, and the current amendments to the claims, with reference to page 8 of the outstanding Office Action, that Katzman in addition discloses such things as powder or granules, suspensions or solutions in water, capsules and tablets and flavorings, different modes of administration, modes of detection of metabolites of the isotopically labelled therapeutically active agent itself, determination of the concentration of metabolites of the therapeutically active agent to adjust dosing regiments, etc, is all irrelevant, as Katzman does not disclose or suggest utilizing any of those components or elements to either track metabolism of

the therapeutically active agent, nor does Katzman teach or suggest use of any of those elements to determine whether a particular patient has or has not taken a particular medication.

Reconsideration and withdrawal of this ground for rejection is therefore respectfully requested.

4. 35 USC §103:

Claims 4, and 5 stand rejected as unpatentable over Katzman in view of Payne (WO98/39470). Applicants respectfully traverse.

The deficiencies in Katzman with respect to disclosure of that which is currently claimed in this application are discussed above. Payne is cited as a disclosure of "a method of detecting conditions by analysis of gases or vapors" including use of "an array of semiconducting organic polymer gas sensors …other types of gas sensors…". As discussed above Katzman does not disclose detection of compliance in taking a medication at all, whether by use of sensor technology or any other means, via sampling of a patient's expired breath. Reiterating briefly, Katzman requires, as a predicate, that a medication is definitely taken prior to initiation of metabolic studies, and, in addition, only monitors metabolites of the API. Per the present invention, it is the taking of the medication which is the unknown item to be determined, and, in addition, the marker is combined with the API for concurrent administration and it is explicitly excluded now that the marker is present in the API itself. Payne is directed to detection of conditions unrelated to compliance with a prescribed medication regimen, Payne, which, while directed to analysis of gases or vapours from a respiring subject, neither discloses nor

suggests use of such a method for measuring compliance in taking a medication. The combination of Katzman and Payne does not create a valid *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Claim 6 is rejected as unpatentable over Katzman in view of Forester. Applicants respectfully traverse. It is unlikely that one skilled in the art would have any reason to combine these references in the absence of Applicants' teachings. The deficiencies of Katzman are discussed above. Claim 6, which depends from claim 1, requires the determination of whether a medication has been taken at all, rather than determination of whether a medication that has definitely been taken is being metabolized, and if so, how quickly. Even if one were to combine Katzman with the cough-drop patent of Forester, Forester does not cure these defects. Therefore, Applicants urge that this rejection should be withdrawn.

Claim 22 is rejected as unpatentable over Katzman in view of Payne and Ueda (5,425,374). Applicants again traverse. The insufficiency of the Katzman/Payne combination of references is discussed above. Ueda, even though it might disclose dehumidification of a sample, does not cure the basic defect in Katzman (which is also not cured by Payne) of failing to teach monitoring of whether a medication is taken of one's own volition (the administration of medication being, according to Katzman, a necessary given). This rejection may therefore also be withdrawn. Reconsideration is respectfully requested.

5. The Examiner's Responses to Arguments Previously Made:

The bottom of pages 12 to page 16 of the latest Office Action outline reasons why Applicants' previous arguments were not considered persuasive. Though Applicants respectfully disagree, they assert that the present response provides an amended set of claims and arguments based on such amendments which clearly distinguish the claimed invention from what is taught in the cited references. For example, in this section of the outstanding Office Action, it is alleged that the "Applicant's recitation to "providing" reads on the recitation in Katzman to "administering", and further, in both cases, as in Applicant's method and Katzman, there is a presumption that the drug/medication is to be taken." As emphasized in the arguments presented above, and as made explicit in the amendment to claim 1, Katzman's "administering" means exactly that - the isotopically labeled therapeutically active agent is given to the patient and there is no doubt as to whether or not the patient has complied in taking the medication or not. In Applicant's invention, while indeed a medication is provided to the patient, the patient's taking or not of that medication is the entire issue - has the patient taken the medication or not, and Applicant's method provides a means for determining this unknown.

Indeed, Applicant's method is not drawn to a random sampling of people, and it is drawn to checking patient compliance in taking medication that has been provided (but not administered!) to the patient. That further dependent claims recite specific routes by which the medication is designed to preferably be taken by the patient in no way makes the "administering" of Katzman, which is a known entity, the same as the providing of the medication to a

patient who may or may not then take that medication according to the designed route, and the compliance in taking of which is then determined according to this invention.

As discussed above, it is respectfully reasserted that isotopically labeling the therapeutically active agent is clearly distinguishable from providing a detectable marker which is provided to a patient in such a form as to be concurrently taken by the patient.

As claim 1 is herein amended to clearly distinguish over Katzman, the dependent claims which are rejected in view of a combination of secondary references with Katzman, which secondary references do not cure the deficiencies in Katzman, are likewise free of that art.

6. Conclusion:

All grounds for objection or rejection having been addressed and overcome herein by amendment of the claims and appropriate arguments in support of those amendments, Applicants urge that the currently amended claim set is in condition for allowance. No new matter has been introduced. Expedited passage of this application to patent is respectfully requested.

In the event that there are any minor issues which the Examiner believes should be addressed prior to passage of this case to allowance, it is respectfully requested that the Examiner telephonically contact the undersigned to discuss appropriate resolution of any such remaining issues.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully submitted,

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